(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 3 906 938 A1**

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
10.11.2021 Bulletin 2021/45

(51) Int Cl.:
A61K 38/38 *(2006.01)* ***A61M 1/34*** *(2006.01)*
A61P 25/28 *(2006.01)*

(21) Application number: **20382375.2**

(22) Date of filing: **07.05.2020**

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
Designated Extension States:
BA ME
Designated Validation States:
KH MA MD TN

(71) Applicant: **Grifols Worldwide Operations Limited**
Dublin 22 (IE)

(72) Inventors:
- **JORBA RIBES, JAVIER**
08174 SANT CUGAT DEL VALLES (BARCELONA) (ES)
- **PAEZ REGADERA, ANTONIO MANUEL**
08174 SANT CUGAT DEL VALLES (BARCELONA) (ES)

(74) Representative: **Durán-Corretjer, S.L.P.**
Còrsega, 329
(Paseo de Gracia/Diagonal)
08037 Barcelona (ES)

(54) COMPOSITION COMPRISING ALBUMIN FOR USE IN THE TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS (ALS) BY PLASMA EXCHANGE

(57) The present invention relates to a composition comprising albumin for use in the treatment of Amyotrophic Lateral Sclerosis (ALS), wherein the composition is administrated to the patient by plasma exchange using a volume of said composition equivalent to approximately 100 % of the volume of plasma withdrawn from the patient, and with a frequency of twice a week the first 3 weeks and once a week for the following 21 weeks, for a total period of 24 weeks.

EP 3 906 938 A1

Description

[0001] The present invention relates to a composition comprising albumin for use in the treatment of amyotrophic lateral sclerosis (ALS) by plasma exchange.

[0002] Amyotrophic lateral sclerosis (ALS) is a motor neurone disease affecting about 3 of 100.000 people a year in United States. ALS is a chronic, progressive and fatal degenerative neurological disease that causes the death of motor neurons controlling voluntary muscles. For 90 % of cases, the origin of the disease is unknown and sporadic. Despite extensive studies on this disease, its pathogenesis has not been identified yet and no effective treatment has been found.

[0003] As previously mentioned, ALS is usually progressive, with upper and lower motor paralysis leading to an average survival of three years from the start of the disease. In general, difficult and distressing medical problems arise during the course of the disease, which have motivated the use of a wide variety of treatments, such as toxic drugs, inactivated cobra venom and plasmapheresis, among others.

[0004] Plasmapheresis is a common medical procedure in which plasma from a patient is separated from whole blood. It has been used to treat patients suffering from different chronic diseases. Once the plasma is separated from the blood cells, the cells can be returned to the patient with or without replacement fluids. During treatment of patients by therapeutic plasmapheresis, a catheter is placed in a major vein, for example in the arm, and a second catheter is placed in another vein, for example, in the foot or hand. The blood then leaves the patient's body through the catheter and is sent to a separating device, where the plasma is separated from the blood cells. Blood without plasma and, optionally, along with replacement fluid, is returned to the patient through the second catheter. Instead of two peripheral catheters, a dual-channel, central, or peripheral catheter can also be used.

[0005] The use of plasmapheresis for the treatment of ALS has been previously reported. For example, Silani et al. used plasma exchange with frozen plasma and saline for the treatment of four ALS patients during six months (Silani, V., Scarlato, G., Valli, G. and Marconi, M. "Plasma Exchange Ineffective in Amyotrophic Lateral Sclerosis" Arch. Neurol. (1980) Vol. 37: 511-513). However said treatment was unsuccessful and did not change the course of the disease. In addition, in a later work of Kelemen et al., the use of plasma exchange with albumin at 5 % in combination with immunosuppressants for the treatment of ALS shown no beneficial effect on the disease, nor any clinical improvement in any of the 4 patients studied (Kelemen, J., Hedlund, W., Orlin, J.B., Berkman, E.M. and Munsat T.L. "Plasmapheresis with immunosupression in Amyotrophic Lateral Sclerosis". Arch. Neurol. (1983), Vol. 40: 752-753.).

[0006] These previous works explain why the use of plasma exchange in the treatment of ALS is considered of category IV (the lower) in the guidelines on the use of therapeutic apheresis in clinical practice by the American Society for Apheresis (Schwartz, J., Winters, J.L., Padmanabhan, A., Balogun, R.A., Delaney, M., Linenberger, M.L., Szczepiorkowski, Z.M., Williams, M.E., Wu, Y., Shaz B.H. "Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue" J. Clin. Apher. 2013 Jul; 28(3):145-284). Category IV relates to disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful.

[0007] More recently, it was shown in the Spanish Patent ES201530074 that the use of a composition comprising albumin for the treatment of ALS by plasma exchange could provide some beneficial effects on the course of the disease. In said Spanish Patent, an ALS patient was treated during 14 weeks with a composition comprising human albumin at 5 % (w/v) by plasma exchange 3 times a week during the 2 first weeks and once a week during the other 12 weeks. The effect of said specific treatment was evaluated using a functional qualification of ALS from a period starting 12 months prior the treatment and finalizing 2 months after the end of the treatment. The results of said functional qualification showed a tendency to stabilization of the course of the disease over time, which was unexpected since it is well known that a ALS patient's condition always tends to worsen.

[0008] However, said study was conducted with only one patient for whom the course of the disease was maintained, but not improved in any way.

[0009] Therefore, there remains a need for a treatment of ALS by plasma exchange that could avoid the normal progression of the disease and could even improve the functional qualification of the patient.

[0010] The inventors of the present invention have surprisingly found that the use of a composition comprising albumin for the treatment of ALS by plasma exchange could indeed improve the progression of the disease by using specific treatment conditions.

[0011] Therefore, in a first aspect the present invention relates to a composition comprising albumin for use in the treatment of ALS by plasma exchange.

[0012] Preferably, the albumin concentration in said composition is between 5 % and 25 % (w/v). More preferably, the concentration of albumin is about 5 %, 10 %, 15 %, 20 % or 25 % (w/v). Even more preferably, the concentration of albumin is about 5 % (w/v).

[0013] Albumin can be either recombinant or purified from human plasma. In a preferred embodiment, the albumin is purified from human plasma.

[0014] In preferred embodiments of the present invention, the composition comprising albumin for use in the treatment of ALS is administrated to a patient in need thereof by plasma exchange using a volume of said composition equivalent to approximately 100 % of the volume of plasma withdrawn from the patient. In preferred embodiments, said composition is administrated to the pa-

tient by plasma exchange twice a week the first 3 weeks and once a week for the following 21 weeks, for a total period of 24 weeks.

[0015] In the present invention, treatment with the composition comprising albumin is preferably carried out by plasma exchange, i.e. said composition comprising albumin is used as replacement liquid and will be returned to the patient along with the blood cells, which have been previously separated from the plasma by plasmapheresis. In general, a determined volume of plasma is withdrawn from the patient and the plasma exchange with the composition comprising albumin is carried out with a volume of said composition equivalent to approximately 100 % of the volume of plasma withdrawn from the patient. A person skilled in the art understands that small variations of approximately ± 10 % of this volume will fall within the scope of the present invention.

[0016] One of the main difference from the use of a composition comprising albumin for the treatment of ALS according to the present invention and the treatments known in the prior art, is that in the present treatment the use of immunosuppressants is not necessary before, during or after finishing said treatment. ALS has been linked in the prior art to abnormalities of the immune system such as abnormalities of surface antigens, T lymphocytes, and macrophage migration (Kelemen J. et al., Above), which may suggest the use of a concomitantly immunosuppressant treatment with any ALS treatment. However, it is demonstrated herein that the use of immunosuppressants is not necessary with the treatment of the present invention to obtain satisfactory results for the treatment of ALS. Thus, in some embodiments, the use of immunosuppressants is not required during the treatment with the composition of the present invention. However, in other embodiments, the use immunosuppressants during the treatment of ALS with the composition of the present invention is also possible if required by other conditions of the patient.

[0017] In the treatment of the present invention, the plasma exchange using the composition comprising albumin as replacement fluid is carried out with a frequency of twice a week the first 3 weeks and once a week during the following 21 weeks, which correspond to a total period of 24 weeks.

[0018] During the duration of the treatment according to the present invention, patients may experience, at least, a tendency to stabilize the course of the disease. In other words, since ALS is a disease whose progression is rapid and gradual once ALS symptoms onset, achieving stabilization of its progression during the duration of the treatment can be considered a very positive result. In addition to that, the treatment of the present invention has also demonstrated to improve the functional qualification of some of the patients and therefore, to reverse the progression of the disease to less advanced stages.

[0019] In a second aspect, the present invention relates to a method for treating ALS in a patient in need thereof, comprising the administration of a composition comprising albumin by plasma exchange. Preferably, said plasma exchange is carried out using a volume of said composition equivalent to approximately 100 % of the volume of plasma extracted from the patient. A person skilled in the art understands that small variations of approximately ± 10 % of this volume will fall within the scope of the present invention. In some preferred embodiments, said method for treating ALS is carried out with a frequency of twice a week the first 3 weeks and once a week during the following 21 weeks, for a total period of 24 weeks.

[0020] Preferably, the albumin concentration in said composition is between 5 % and 25 % (w/v). More preferably, the concentration of albumin is about 5 %, 10 %, 15 %, 20 % or 25 % (w/v). Even more preferably, the concentration of albumin is about 5 % (w/v).

[0021] Albumin can be either recombinant or purified from human plasma. In a preferred embodiment, the albumin is purified from human plasma.

[0022] In some embodiments, the use of immunosuppressants is not required during the method for treating ALS of the present invention.

[0023] Hereinafter, the present invention is described in more detail with reference to illustrative examples, which does not constitute a limitation of the present invention.

EXAMPLE

[0024] Plasma exchange (PE) with albumin 5 % (Albutein®, Grifols, S.A., Spain) in patients diagnosed with ALS.

[0025] Men and women aged 18 to <70 years with a definite, possible or probable diagnosis of ALS according to El Escorial/Airlie House criteria, and having a forced vital capacity (FVC) >70 % of predicted value were eligible for a prospective, single-arm, single-center, pilot study.

[0026] Patients underwent 6-month of PE-treatment using 5 % albumin (Albutein® 5 %) in 2 phases: one intensive phase involving 2 PE sessions per week for 3 weeks, followed by a maintenance phase involving one PE session per week for 21 weeks. The follow-up period was 6-month.

[0027] Endpoints were changes in Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score and FVC. Based on the typical survival of 3-5 years from time of ALS symptoms onset, and the typical decrease of 1 point/month in the ALSFRS-R overall score, three categories of disease progression were defined: "normal", "slow", and "fast", depending on whether ALSFRS-R slope was between -0.8 and -1.33 points/month, < -0.8 points/month, or > -1.33 points/month, respectively.

[0028] Thirteen adults with ALS were enrolled and evaluated. Median (IQR) overall score at baseline was 42.0 (37.0, 44.0). ALSFRS-R score declined throughout the study, although the median decline was less than

expected in untreated patients. Seven patients at the end of treatment and 5 patients at the end of study had a slower decline than expected. Six patients remained in the same "progressor" category while 4 improved their category at the end of the treatment. Median (IQR) of FVC and predicted FVC percentage at baseline were 3.9 (3.0, 4.9) L and 87.0 % (76.0, 96.0), respectively. Median FVC decreased significantly during the study. The treatment was well tolerated.

[0029] Plasma Exchange with albumin replacement was safe and well tolerated in ALS patients. Although functional impairment progressed, most patients showed a slower than expected rate of decline at the end of treatment. In terms of slope progression most patients either remained stable (54.5 %) or improved (36.4 %) their category.

[0030] Thus, the treatment of the present invention has been proved not only to stabilize the course of the disease but also to improve the conditions of the patients and therefore, to reverse the progression of the disease to less advanced stages.

[0031] Although the invention has been described with respect to a preferred embodiment, this should not be considered as limiting the invention, which will be defined by the broadest interpretation of the following claims.

Claims

1. Composition comprising albumin for use in the treatment of Amyotrophic Lateral Sclerosis (ALS) in a patient in need thereof, wherein the composition is administrated to said patient by plasma exchange using a volume of said composition equivalent to approximately 100 % of the volume of plasma withdrawn from the patient, and with a frequency of twice a week the first 3 weeks and once a week for the following 21 weeks, for a total period of 24 weeks.

2. Composition for use, according to claim 1, wherein the concentration of albumin in the composition is between 5 % and 25 % (w/v).

3. Composition for use, according to claim 2, wherein the concentration of albumin in the composition is about 5 % (w/v).

4. Composition for use, according to any one of claims 1 to 3, wherein the albumin is recombinant or purified from human plasma.

5. Composition for use, according to any one of claims 1 to 4, wherein the use of immunosuppressants is not required.

6. Method for treating Amyotrophic Lateral Sclerosis (ALS) in a patient in need thereof, comprising the administration of a composition comprising albumin by plasma exchange using a volume of said composition equivalent to approximately 100 % of the volume of plasma withdrawn from the patient, and with a frequency of twice a week the first 3 weeks and once a week for the following 21 weeks, for a total period of 24 weeks.

7. Method, according to claim 6, wherein the concentration of albumin in the composition is between 5 % and 25 % (w/v).

8. Method, according to claim 7, wherein the concentration of albumin in the composition is about 5 % (w/v).

9. Method, according to any one of claims 6 to 8, wherein the albumin is recombinant or purified from human plasma.

10. Method, according to any one of claims 6 to 9, wherein the use of immunosuppressants is not required.

Europäisches Patentamt
European Patent Office
Office européen des brevets

EUROPEAN SEARCH REPORT

Application Number
EP 20 38 2375

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
Y,D	ES 2 535 579 A1 (GRIFOLS WORLDWIDE OPERATIONS LTD [IE]) 12 May 2015 (2015-05-12) * claims; figure 1; examples * -----	1,2,4-7, 9,10	INV. A61K38/38 A61M1/34 A61P25/28
Y	Instituto Grifols ET AL: "Study Details Tabular View Study Results Disclaimer How to Read a Study Record Efficacy and Safety of Plasma Exchange With Albumin in Patients With Amyotrophic Lateral Sclerosis Sponsor: Study Description Amyotrophic Lateral Sclerosis Biological: Albumin Phase 2 Go to", , 24 June 2015 (2015-06-24), XP055738310, Retrieved from the Internet: URL:https://clinicaltrials.gov/ct2/show/NCT02479802 [retrieved on 2020-10-09] * the whole document * -----	1,2,4-7, 9,10	
Y	WO 2014/159247 A1 (UNIV FLORIDA [US]) 2 October 2014 (2014-10-02) * page 1 - page 2; example 2 * * page 33, line 1 - line 12 * -----	1,2,4-7, 9,10	TECHNICAL FIELDS SEARCHED (IPC) A61K A61M A61P
	-/--		

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	12 October 2020	Langer, Astrid

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

Europäisches Patentamt
European Patent Office
Office européen des brevets

EUROPEAN SEARCH REPORT

Application Number
EP 20 38 2375

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	ADRIANO CHIÒ ET AL: "Amyotrophic Lateral Sclerosis Outcome Measures and the Role of Albumin and Creatinine : A Population-Based Study", JAMA NEUROLOGY, vol. 71, no. 9, 1 September 2014 (2014-09-01), page 1134, XP055738304, US ISSN: 2168-6149, DOI: 10.1001/jamaneurol.2014.1129 * Abstract, Conclusion; page 1140; figures * -----	1-10	
A	WO 2020/018343 A1 (ALKAHEST INC [US]) 23 January 2020 (2020-01-23) * page 20, line 4 - line 17; example 1 * -----	1-10	

TECHNICAL FIELDS SEARCHED (IPC)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	12 October 2020	Langer, Astrid

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 20 38 2375

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

12-10-2020

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
ES 2535579 A1	12-05-2015	NONE	
WO 2014159247 A1	02-10-2014	AU 2014241078 A1	08-10-2015
		AU 2020202852 A1	21-05-2020
		CA 2904960 A1	02-10-2014
		EP 2970884 A1	20-01-2016
		HK 1220227 A1	28-04-2017
		JP 6628285 B2	08-01-2020
		JP 2016515208 A	26-05-2016
		JP 2020055827 A	09-04-2020
		US 2016025747 A1	28-01-2016
		US 2019285652 A1	19-09-2019
		WO 2014159247 A1	02-10-2014
WO 2020018343 A1	23-01-2020	NONE	

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- ES 201530074 **[0007]**

Non-patent literature cited in the description

- **SILANI, V. ; SCARLATO, G. ; VALLI, G. ; MARCONI, M.** Plasma Exchange Ineffective in Amyotrophic Lateral Sclerosis. *Arch. Neurol.,* 1980, vol. 37, 511-513 **[0005]**
- **KELEMEN, J. ; HEDLUND, W. ; ORLIN, J.B. ; BERKMAN, E.M. ; MUNSAT T.L.** Plasmapheresis with immunosupression in Amyotrophic Lateral Sclerosis. *Arch. Neurol.,* 1983, vol. 40, 752-753 **[0005]**
- **SCHWARTZ, J. ; WINTERS, J.L. ; PADMANABHAN, A. ; BALOGUN, R.A. ; DELANEY, M. ; LINENBERGER, M.L. ; SZCZEPIORKOWSKI, Z.M. ; WILLIAMS, M.E. ; WU, Y. ; SHAZ B.H.** Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue. *J. Clin. Apher.,* July 2013, vol. 28 (3), 145-284 **[0006]**